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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,107	11/20/2003	Michael P. Girouard	P03155US (98554.1P3)	8886

22920 7590 04/01/2009

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EXAMINER	
CHUI, MEI PING	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
04/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,107	GIROUARD, MICHAEL P.	
	Examiner	Art Unit	
	MEI-PING CHUI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,85,91,117,119,124 and 138-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,85,91,117,119,124 and 138-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *n/a*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on 07/11/2008 is acknowledged. Claims 55 and 119 have been amended, claims 85, 91, 117, 124 are previously presented; claims 1-54, 56-84, 86-90, 92-116, 118, 120-123, 125-137 have been cancelled previously cancelled; new claims 138-143 are added.

Status of Claims

Accordingly, claims 55, 85, 91, 117, 119, 124 and 138-143 are presented for examination on the merits for patentability.

Rejection(s) not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

It is noted to the Applicants that claim(s) has been cancelled in this application is not included in the following rejections, and new claims are included in the following rejections.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55, 85, 91, 117, 119 and 124 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(**1**) Claims 55, 85, 91, 117, 119 and 124 recite the term "substantially pure", which is a relative term. Although the instant specification discloses the purity of estrone oleate and estrone eicosenoate; however, the recitation of the substantially pure constituents are for the 2-hydroxy estrone or estrogen derivatives monoester. Since the specification does not provide a standard for ascertaining the metes and bounds of how pure is considered to be substantially pure for the 2-hydroxy estrone or estrogen derivatives monoester; hence, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and claims are, therefore, rendered indefinite.

The rejection with respect to claims 55, 85, 91, 117, 119 and 124, under 35 U.S.C. 112, second paragraph, as being indefinite, are maintained.

Response to the Arguments

Applicant argues that the language "substantially pure" is sufficiently definite to one skilled in the art. Applicant also refers the references in the examples to 80 % purity (see page 12, lines 23-26), 98 % (see page 6, lines 30-32), and 2-hydroxyestrone (see page 49, lines 21-23).

Applicant's arguments filed on 07/11/2008 have been fully considered but they are not persuasive. Applicant argues that the purity of the recited fatty acid monoester of 2-hydroxyestrogen, especially 2-hydroxyestrone or 2-hydroxyestradiol, and a fatty acid is disclosed and can be found on page 12, lines 23-26 of the instant specification; however, the disclosed

compounds, which are 81 % and 80 % pure, on page 12, lines 23-26 refer to estrone oleate and estrone eicosenoate, respectively. Since these two compounds do not contain hydroxyl functionality at the C2 position, their purity cannot represent the purity of the claimed 2-hydroxy estrone or estrogen derivatives monoester.

Similarly, Applicant points out that the purity of the recited fatty acid monoester compound has sufficient support and is disclosed in page 6, lines 30-32. However, the disclosed compound, which is 98 % pure, is refers to 2-bromoestrone ester of cis-11-eicosenoate, not of the claimed 2-hydroxy estrone or estrogen derivatives monoester.

(**2**) Claims 55, 117, 119 and 124 recite the term "derivative". The term "derivative" is defined, according to Merriam-Webster's Collegiate Dictionary (tenth Edition), as a chemical substance related structurally to another substance and theoretically derivable from it, or a substance that can be made from another substance (see page 311, derivative (n): meaning 4 and 5). However, the term "derivative" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree; it is unclear that the term "derivative" means a structural derivative or a functional derivative in relation to the recited estrogens, 2-hydroxyestrone or 2-hydroxyestradiol. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and thus rendering the claim indefinite.

The rejection with respect to claims 55, 117, 119 and 124, under 35 U.S.C. 112, second paragraph, as being indefinite, are maintained.

Response to the Arguments

Applicant argues that the term derivative is commonly used in the art, thus one ordinary skill in the art would know what it means and what the claims are covered (see Remarks: page 5).

Applicant's argument filed on 07/11/2008 has been fully considered but they are not persuasive because the term "derivative" means a structural derivative or a functional derivative in relation to the recited estrogens, 2-hydroxyestrone or 2-hydroxyestradiol. Since not only the structural variants of 2-hydroxyestrone monoester or 2-hydroxy estrogen monoester can be referred as derivatives, functional variants of 2-hydroxyestrone monoester or 2-hydroxy estrogen monoester, which may include any compound that is known or will be known to possess an effect for lowering body weight in a mammal, can also be referred to as derivatives. Since the metes and bounds of such "derivatives" cannot be clearly defined, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and the claims are therefore indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 55, 85, 91, 117, 119, 124 and 138-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alemany et al. (U. S. Patent No. 5,798,348) in view of Allison et al. (U. S. Patent Application Publication No. 2006/0083778), and further in view of Zhu et al. (Carcinogenesis, 1998, 19, page 1-27).

Applicant Claims

Applicant claims a method of lowering body weight in a mammal, i.e. human, comprises administering an effective amount of substantially pure fatty acid monoester, or a precursor thereof, of an estrogen and a fatty acid in combination with an amount of at least one pharmaceutically acceptable excipients or cosmetically acceptable excipients; wherein the estrogen is a 2-hydroxy derivative of estrone, diethylstilbestrol, estriol, estradiol or ethinyl estradiol, and the fatty acid consists of more at least 20 carbon atoms, with the proviso that the estrogen is steroidal and has a hydroxyl group at the C-3 position, where the fatty acid is conjugated with the steroid ring system through an acyl bond.

Determination of the scope and content of the prior art
(MPEP 2141.01)

Alemany et al. teach a method for lowering the body weight in a mammal comprising the step of administering to said mammal an effective amount of a substantially pure fatty acid monoester of an estrogen and a fatty acid (column 1, line 6-8; column 2, line 16-18; column 3, line 34-36; and column 8, claim 15), wherein the estrogen is estrone, diethylstilbestrol, estriol, estradiol or ethinyl estradiol (column 1, line 57-59 and column 8, claims 1, 6 and 7) and the fatty acid is oleic acid (a fatty acid with 18 carbon atoms) or arachidonic acid (a fatty acid with 20 carbon atoms) (column 1, line 60-63; column 2, line 7-9; column 7, claims 1, 6 and 7).

Alemany et al. also teach that the fatty acid moiety and the estrogen moiety of the estrogen fatty acid monoester is linked by an ester linkage, where the acyl group of the fatty acid is attached to the C-3 hydroxyl group of the estrogen (column 2, line 10-12; column 7, claims 1, 6-7 and 20 and column 8, claim 15).

Alemany et al. further teach that the estrogen fatty acid monoester is administered in combination with an amount of at least one member selected from the group consisting of pharmaceutically acceptable excipients and cosmetically acceptable excipients which amount is sufficient for the purposes thereof (column 8, claim 15).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

However, Alemany et al. do not teach that the estrogen moiety of the estrogen fatty acid monoester contains a hydroxyl group at the C-2 position. However, the deficiency is cured by the teachings of Allison et al. and Zhu et al.

Allison et al. teach a treatment method comprising the step of administering a formulation to an individual containing an estradiol metabolite in liposomes (page 11, claim 35).

Allison et al. teach that estradiol is converted into different derivatives through metabolic processes in vivo to form estradiol metabolites, i.e. catecholestrogens (catechol contains two hydroxyl groups at C2 and C3 position of the phenyl ring). Allison et al. also teach that the catecholestrogen, i.e. 2-hydroxyestradiol, is formed by hydroxylation of estrogen via cytochrome P450 enzymes (page 1, paragraph 0003, lines 1-6).

Allison et al. teach that the estradiol metabolite of use can be 2-hydroxyestradiol, which has been reported to have effects on number of cellular processes. Allison et al. also teach that 2-hydroxyestradiol has been shown to affect cholesterol levels in ovariectomized rats, to inhibit adipose cell proliferation in culture and to decrease the effects of obesity and metabolic syndrome (page 1, paragraph 0004, lines 1-10).

Zhu et al. teach that 2-hydroxylation of estrone to 2-hydroxyestrone is a major metabolic pathway that occurs in the liver by cytochrome P450 hydroxylase.

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to a person of ordinary skilled in the art at the time the invention was made to combine the teachings of Alemany et al. and Allison et al. and Zhu et al. to utilize a 2-hydroxyestrogen, i.e. 2-hydroxyestrone or 2-hydroxyestradiol, of fatty acid monoester to lower the body weight of a mammal to arrive at the instant invention.

One of ordinary skill would have been motivated to do this because it has been taught in the art by Alemany et al. that administration of estrone fatty acid monoester can lower the body weight in a mammal and it is also taught in the arts that 2-hydroxlestradiol which is a metabolite of estradiol can decrease the effects of obesity and inhibits adipose cell proliferation; similarly, 2-hydroxyestrone is a metabolite of estrone forming from the same mechanism in vivo by P450 cytochrome enzymes. Furthermore, the art, namely Alemany et al., already establish the concept of linking a fatty acid, i.e. arachidonic acid (it is a fatty acid consists of 20 carbon atoms) to an estrogen at the C-3 position of the estrogen in methods of lowering body weight in a mammal. Therefore, the instant application links a fatty acid consists of at least 20 carbon atoms to a 2-hydroxy estrogen, with the same method utility is obvious and would expect to behave the same manner for lowering body weight in a mammal.

Therefore, the Examiner can only conclude that it would be obvious to administer a fatty acid monoester of 2-hydroxy estrogen, i.e. 2-hydroxyestrone or 2-hydroxyestradiol in a method of lowering body weight in a mammal because 2-hydroxyestrone or 2-hydroxyestradiol are functional equivalent estrogenic metabolites formed from the same mechanism by cytochrome P450 enzymes, and thus can be used interchangeably. The pharmaceutically acceptable excipients or cosmetically acceptable excipients is a routine practice, as taught by Alemany et al. and Allison et al., which would be dependent on the formulation of intended use.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection with respect to claims 55, 85, 91, 117, 119, 124 and 138-143 under 35 U.S.C. 103(a) is maintained.

Response to the Arguments

Applicant's argument filed on 07/11/2008 has been fully considered but they are not persuasive.

Applicant first argues that the prior art Alemany et al. discloses fatty acid of 18 or fewer carbon molecules whereas the instant composition claims the fatty acid contains at least 20 carbon atoms (See: Remarks: page 6).

The argument is not persuasive because Alemany et al. not only teach the fatty acids having 18 carbon atoms, Alemany et al. also clearly teach the use of arachidonic acid, which is a fatty acid with 20 carbon atoms. Since the instant claims recite the fatty acid having at least 20 carbon atoms, which includes a fatty acid having 20 carbon atoms, the teaching of Alemany et al. meets the claimed limitation of "fatty acid having at least 20 carbon atoms".

Applicant also argues that the reference Allison et al. is not available as a prior art because Allison et al. is published on 04/20/2006 (See Remarks: page 6).

The argument is not persuasive because the present application claims the benefit of an earlier U. S. provisional application dating back to November 20, 2002. Allison et al. et al., on the other hand, filed on 04/25/2003, which claimed the benefit of a provisional application dating

back on 05/02/2002 and published on 04/20/2006. Since the reference Allison et al. is filed before the effective U. S. filing date of the present application and published after the effective U. S. filing date of the present application, it qualifies as a 102(e) prior art, and can be used in a rejection under 35 U.S.C. § 103(a) based on § 102(e) prior art.

Applicant next argues that the reference Zhu et al. continually suggests and teaches additional research in order to determine the significance, to advance the knowledge and to ascertain the physiological significance of biochemical functions cannot provide a valid basis for a rejection of Applicant's invention as claimed. There is no explicit or implied teaching, suggestion, or motivation for one of ordinary skill in the art to do anything other than more research (see Remarks: page 8).

The argument is not persuasive because the goal of the reference Zhu et al. is only to reconfirm the teaching of Allison et al., which teach the catecholestrogen, i.e. 2-hydroxyestradiol, is formed by hydroxylation of estrogen via cytochrome P450 enzymes, and where Zhu et al. also teach that the 2-hydroxylation of estrone to 2-hydroxyestrone is a major metabolic pathway that occurs in the liver by cytochrome P450 hydroxylase. There is no other teaching of Zhu et al. has been made in the rejection.

In summary, the combined teaching of Alemany et al. teach the administration of estrone fatty acid monoester for lowering the body weight in a mammal and Allison et al. teach 2-hydroxlestradiol is a metabolite of estradiol, which has decreasing effect on obesity and can inhibit adipose cell proliferation. Similarly, 2-hydroxyestrone is a metabolite of estrone forming from the same mechanism in vivo by P450 cytochrome enzymes as 2-hydroxyestradiol. Furthermore, the prior art, namely Alemany et al., has already established the concept of linking

a fatty acid, i.e. arachidonic acid (it is a fatty acid consists of 20 carbon atoms) to an estrogen at the C-3 position of the estrogen in methods of lowering body weight in a mammal. Therefore, the instant invention links a fatty acid consisting of at least 20 carbon atoms to a 2-hydroxy estrogen that is used for the same purpose of lowering body weight of a mammal would have been obvious to one of ordinary skill in the art.

Conclusion

No claims are allowed.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be

reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/M. C./

Examiner, Art Unit 1616

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616